RESEARCH ON IMIDAZOLES

XXXV. Thiazolo[3,2-b]benzimidazole and some of its Derivatives*

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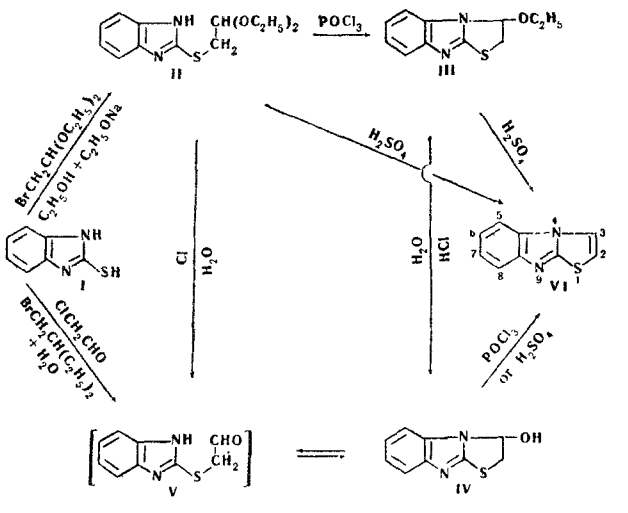
The reactions of 2-mercaptobenzimidazole and 5,6-dimethyl-2-mercaptobenzimidazole with chloroacetaldehyde, bromoacetaldehyde diethylacetal, and α-bromopropionaldehyde are studied. Thiazolo[3,2-a]benzimidazole and some of its derivatives are synthesized

The tricyclic system of thiazolo[3,2-a]benzimidazole (VI) has been little investigated. Thiazolino[3,2-a]benzimidazole [8] and its methylene derivatives [3–7], thiazolino[3,2-a]benzimidazole [8], and some substituted VIs [9–13] have been synthesized by reacting 2-mercaptobenzimidazole (I) with chloroacetic acid (or its esters), dichloroethane, halogenoketones, and propargyl bromide with subsequent cyclization of the intermediate S derivatives I. The 6(7)-hydroxy derivative VI has also been obtained by reacting 2-aminothiazole with p-quinone.

A series of papers [15–18] on the synthesis of imidazole-thiazole condensed systems for the purpose of obtaining the unsubstituted tricyclic system VI and some derivatives of it, investigated the reaction of I with α-halogenoaldehydes and their acetals.

Most detailed studies have been made of the products of reaction of I with chloroacetaldehyde and bromoacetaldehyde diethylacetal (bromoacetal) and the conversions which they undergo when treated with acid reagents ($POCl_3$, HCl, H_2SO_4).



Reaction of I with bromoacetal in ethanol in the presence of sodium ethoxide gives benzimidazolyl-2-mercaptoacetaldehyde diethylacetal (II), characterized as its picrate. As in the case of 4(5)-phenylimidazolyl-2-mercaptoacetaldehyde acetals [15], boiling II with $POCl_3$ splits out a molecule of ethanol, and cyclizing it to 3-ethoxythiazolino[3,2-a]benzimidazole (III). III was also isolated as the picrate after heating II in aqueous ethanol, and by heating II picrate above 140°.

Reaction of I with bromoacetal in water, with the hydrated dimer of dichloroacetaldehyde in various solvents (water, ethanol, dimethylformamide), or saponification of II and III with hydrochloric acid gives one and the same crystalline substance, whose elementary composition is that of benzimidazolyl-2-mercaptoacetaldehyde (V), but whose chemical and physicochemical properties quickly show it to be a tautomeric form of V, 3-hydroxythiazolino[3,2-a]benzimidazole (IV). Like analogous compounds in the 2-mercapto- and 4(5)-mercaptoimidazoles series [15–17], IV (or V) does not give some of the characteristic reactions of the carbonyl group. Only by heating in acetic acid solution was it possible to prepare the 2,4-dinitrophenylhydrazone derivative of the aldehyde V.

The IR spectra* (figure) of compounds IV and IX were observed on the solids (vaseline mulls) and did not show the CO absorption band in the 1650–1750 cm^{-1} region, while there were bands (3060–2680 cm^{-1}) obviously due to OH group valence vibrations. The spectrum of ethoxy compound III did not show valence vibration bands of groups CO, NH, and OH. Unlike IV, 2-acetonylmercaptobenzimidazole hydrochloride [12] has a sharp CO group valence vibrations band (1726 cm^{-1}).

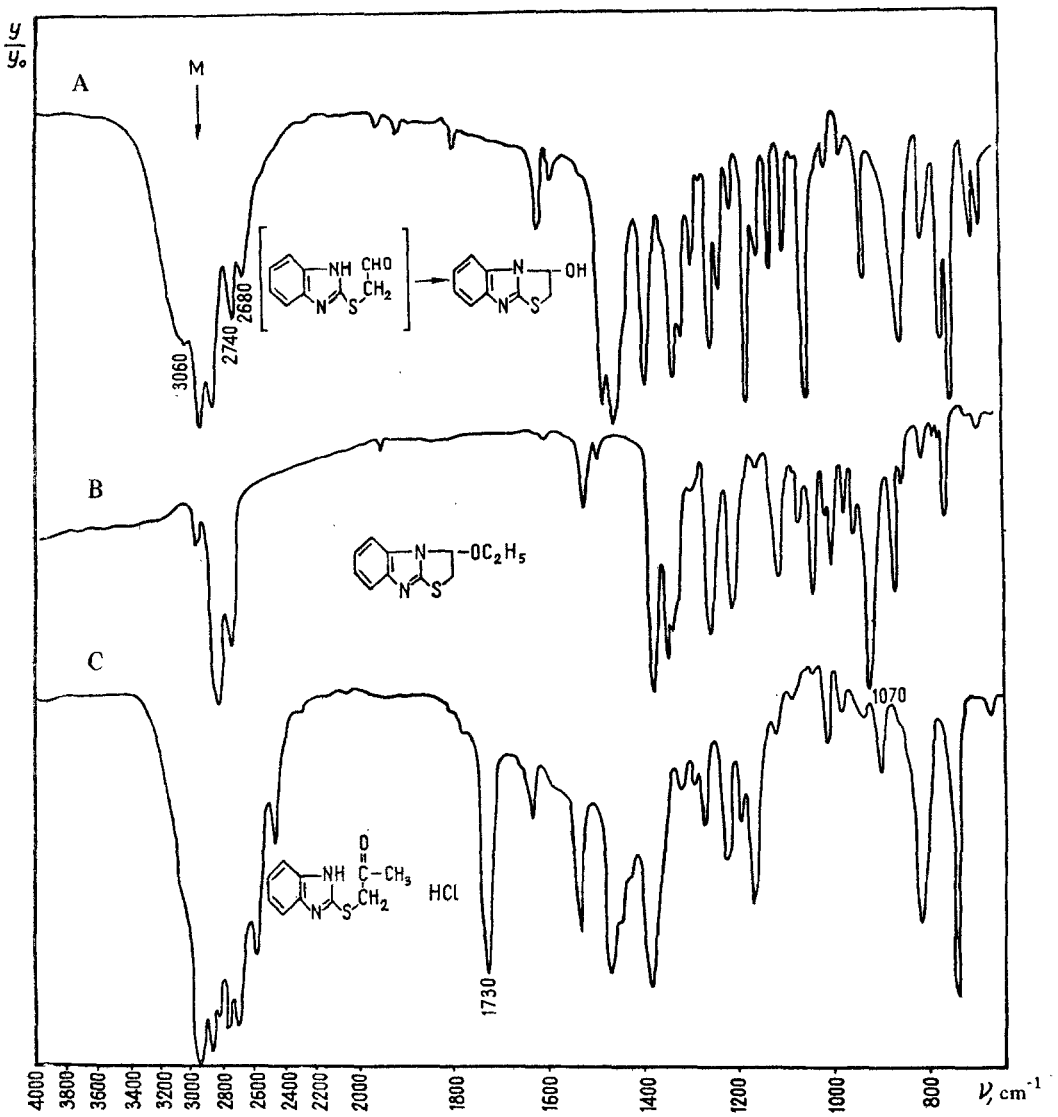
Heating with conc HCl does not change IV, but treatment with $POCl_3$ or conc H_2SO_4, readily removes a molecule of water even in the cold, giving an almost quantitative yield of unsubstituted VI. Compound VI is also formed when II or III is treated with conc H_2SO_4. Treatment of VI with alkyl halides gives the quaternary salts (VII, VIII).

Reaction of I with α-bromopropionaldehyde diethylacetal, followed by dehydration of the 2-methyl-3-hydroxythiazolino[3,2-a]benzimidazole (IX) with conc H_2SO_4 gives 2-methyl[3,2-a]benzimidazole (X).

Like the conversion of I, reaction of 5,6-dimethyl-2-mercaptobenzimidazole (XI) with chloroacetaldehyde

*For Part XXXIV see [18].

*The IR spectra were determined with a UR-10 instrument by E. M. Peresleni and Yu. I. Pomerantsev and we take this opportunity of thanking them.



IR spectra:
A) IV. B) IX. C) III.

and the diethylacetals of bromoacetaldehyde and bromopropionaldehyde gives compounds XII–XVI.

EXPERIMENTAL

Benzimidazolyl-2-mercaptoacetaldehyde diethylacetal (II). A solution of NaOEt was prepared from 0.92 g Na and 50 ml absolute EtOH, and 6 g I [19] followed by 8.1 g freshly-distilled bromoacetal. The mixture was refluxed for 10–11 hr, left overnight, poured into water, extracted with ether, the extract washed with water, dried over $MgSO_4$, and the solvent vacuum distilled off. Yield 10–10.3 g (94–96.9%). When larger lots were run, the EtOH was vacuum distilled off, the residue dissolved in $CHCl_3$ or ether, and worked up in the way described above. Dark brown liquid, becoming viscous at 18–20°, soluble in organic solvents, insoluble in water, decomposed on attempting to vacuum distil it. The picrate was obtained by mixing ether solutions of base II and picric acid. It was purified by precipitating with water from a cold EtOH-Me_2CO (2:1) solution (heating gives the picrate of base III). Orange-yellow prisms mp 132–136° (bath heated to 128–130°), solidified 138–140°, remelted 209–211° (conversion to picrate III), resolidified at 213–215°, and then remelted 235–236° (conversion to picrate VI). Found: C 46.07; H 4.26; N 13.80; S 6.78%, calculated for $C_{13}H_{18}N_2O_2S \cdot C_6H_3N_3O_7$: C 46.05; H 4.27; N 14.14; S 6.47%.

3-Ethoxythiazolino[3, 2-a]benzimidazole (III). a) A solution of 5.33 g II and 15 ml freshly-distilled $POCl_3$ was refluxed for 1 1/2 hr, the solvent vacuum distilled off, water added to the residue (cooling), the solution then neutralized with $NaHCO_3$, and the mixture extracted with $CHCl_3$. Yield 3.45 g (78.3%), mp 83–87°, colorless long prisms, mp 102.5–103.5° (ex EtOH-H_2O 1:2), soluble in organic solvents, insoluble in water. Found: C 60.03; H 5.36; N 12.74; S 14.36%, calculated for $C_{11}H_{12}N_2OS$: C 59.97; H 5.49; N 12.72; S 14.55%. Picrate, yellow long needles, mp 209–211° (ex EtOH), resolidified 213–215°, remelted 235–236° (conversion to picrate VI). Found: C 45.15; H 3.30; N 15.77; S 7.09%, calculated for $C_{11}H_{12}N_2OS \cdot C_6H_3N_3O_7$: C 45.43; H 3.36; N 15.58; S 7.13%.

b) 1 g II was heated in 50% aqueous EtOH, the solution cooled and treated with aqueous picric acid, to give a picrate, (mp 209–211°), identical with the picrate of III prepared as described in (a).

c) About 0.1 g picrate of II was heated in a capillary to 140–150°, it melted, solidified, and was cooled again, after which it had mp 209–211°.

3-Hydroxythiazolino[3, 2-a]benzimidazole (IV). a) A mixture of 1.5 g I, 0.88 g chloroacetaldehyde dimer hydrate (or the corresponding quantity of the aldehyde itself, as a 20–30% aqueous solution), and 15 ml water was refluxed for 4 hr (ultimately with active charcoal), the solution filtered, cooled, 20 ml water added, and made alkaline with $NaHCO_3$. The precipitate was filtered off, 20 ml water added, and washed with water, yield 1.82 g (94.8%), mp 192–194°. Colorless prisms, mp 194–196° (decomp., ex EtOH), soluble in organic solvents. Found: C 56.35; H 4.13; N 14.63; S 16.53%, calculated for $C_9H_8N_2OS$: C 56.23; H 4.20; N 14.57; S 16.67%. Hydrochloride, colorless needles mp 184–186° (decomp., ex dioxane-water 5:1), soluble in water and lower alcohols, soluble with difficulty in acetone and dichloroethane. Found: Cl 15.74%, calculated for $C_9H_8N_2OS \cdot HCl$: Cl 15.50%. Picrate, yellow needles, mp 225–226° (decomp., ex EtOH). Found: C 42.83; H 2.71; N 16.82; S 7.82%, calculated for $C_9H_8N_2OS \cdot C_6H_3N_3O_7$: C 42.76; H 2.63; N 16.62; S 7.61%. IV was also obtained in high yield (89–93%) when the reaction was carried out in EtOH (4 hr reflux), or dimethylformamide (1 hr at 60–65°, and 10 min at 100°).

b) A mixture of 0.75 g I, 1 g bromoacetal, and 20 ml water was refluxed for 3 hr (ultimately with active charcoal), the solution filtered, cooled, and neutralized with $NaHCO_3$, yield 0.69 g (71.1%), mp 193–195° (decomp.).

c) A solution of 2 g II in 10 ml 36% HCl was refluxed for 1 1/2 hr, cooled, 7 ml water added, and the precipitate filtered off, yield of IV hydrochloride 1.4 g (81.5%), mp 183–184° (decomp.) IV hydrochloride was also obtained from II by carrying out the reaction in ethanolic HCl (18–20°, 3 days), or acetone-conc HCl (18–20°, 5–10 min), mp 183–185°.

d) A solution of 0.1 g III in 2.5 m. conc. HCl was refluxed for 30 min, cooled, 8 ml water added, and the mixture neutralized with $NaHCO_3$, yield 0.07 g (80%), mp 194–196° (decomp).

Benzimidazolyl-2-mercaptoacetaldehyde 2, 4-dinitrophenylhydrazone (V). A solution of 0.5 g IV and 0.5 g 2, 4-dinitrophenylhydrazine in 30 ml glacial AcOH was refluxed for 30 min (ultimately with active charcoal), the products filtered, cooled, and the precipitate filtered off. Reddish brown needles, mp 185–186° (decomp., ex AcOH). Found: C 48.30; H 3.35; S 8.67%, calculated for $C_{15}H_{12}N_6O_4S$: C 48.38; H 3.25; S 8.64%.

Thiazolo[3, 2-a]benzimidazole (VI). a) A solution of 3.84 g IV in 20 ml $POCl_3$ was refluxed for 30 min, the solvent vacuum distilled off, the residue dissolved in water, neutralized with $NaHCO_3$, the precipitate filtered off, and washed with water, yield 3.2 g (92%), colorless needles, mp 141.5–142.5° (ex 15% aqueous EtOH), readily soluble in organic solvents. Found: C 61.83; H 3.27; N 16.28; S 18.28%, calculated for $C_9H_6N_2S$: C 62.04; H 3.47; N 16.08; S 18.41%. Hydrochloride, elongated plates, mp 193–194° (decomp., ex absolute EtOH). Found: Cl 16.78%, calculated for $C_9H_6N_2S \cdot HCl$: Cl 16.83%. Picrate, yellow needles, mp 235–236° (decomp., ex EtOH). Found: C 44.78; H 2.29; N 17.67; S 8.09%, calculated for $C_9H_6N_2S \cdot C_6H_3N_3O_7$: C 44.66; H 2.25; N 17.36; S 7.95%.

b) A solution of 0.96 g IV in 5 ml 96% H_2SO_4 was heated for 15 min at 30°, then left for 3 hr at 18–20°, the products poured into 20 ml water, and neutralized with $NaHCO_3$, yield 0.83 g (95.4%), mp 140–142°.

c) A solution of 2 g II in 4 ml conc H_2SO_4 was heated and the product worked up as in part (b), to give VI mp 138–140°, picrate mp 234–236° (decomp.)

d) A solution of 0.5 g III in 4 ml conc H_2SO_4 was heated for 5 min at 35°, and left overnight at 18–20°. The product was then worked up as described in part (b). Yield 0.38 g (97.4%), mp 140–142°.

Thiazolo[3, 2-a]benzimidazole methiodide (VII). A solution of 1.76 g VI and 2.84 g MeI in 20 ml acetone was refluxed for 1 hr, the products cooled, 30 ml ether added, and the precipitate filtered off, colorless plates mp 237–239° (decomp., precipitated by ether from EtOH, readily soluble in water and EtOH. Found: C 37.50; H 3.28; I 39.92; N 8.84; S 10.21%, calculated for $C_{10}H_9IN_2S$: C 37.99; H 2.87; I 40.14; N 8.86; S 10.14%.

Thiazolo[3, 2-a]benzimidazole methiodide (VIII). Prepared similarly to **VII.** Colorless rhombic plates, mp 214–216° (decomp., precipitated with ether from EtOH). Found: 37.85%, calculated for $C_{11}H_{11}IN_2S$: I 38.44%.

2-Methyl-3-hydroxythiazolino 3, 2-a benzimidazole (IX). A mixture of 3 g I, 4.6 g α-bromopropionaldehyde diethylacetal, and 30 ml water was heated and worked up as described above for IV (b). Yield 3.95 g (95.9%) colorless cubic prisms, mp 196–197° (decomp., ex 50% aqueous EtOH), soluble in most organic solvents. Found: C 58.01; H 4.86; N 13.44; S 15.16%, calculated for $C_{10}H_{10}N_2OS$: C 58.23; H 4.89; N 13.58; S 15.55%. Picrate, yellow crystals, mp 179–180° (decomp. ex 50% aqueous EtOH). Found: N 15.75%, calculated for $C_{10}H_{10}N_2OS \cdot C_6H_3N_3O_7$: N 16.09%.

2-Methylthiazolo[3, 2-a]benzimidazole (X). A solution of 1.75 g IX in 5 ml conc H_2SO_4 was left overnight at 18–20°, and the product worked up as described for IV (b). Yield 1.53 g (96.2%), mp 154–156°, colorless prisms, mp 157–158° (ex EtOH-water, 1:2), soluble in organic solvents. Found: C 63.75; H 4.41; N 14.60; S 17.14%, calculated for $C_{10}H_8N_2S$: C 63.80; H 4.28; N 14.88; S 17.03%. Picrate, yellow plates, mp 247–248° (decomp., ex EtOH). Found: N 17.39%, calculated for $C_{10}H_8N_2S \cdot C_3H_6N_3O_7$: N 16.78%.

5, 6-Dimethylbenzimidazol-2-mercaptoacetaldehyde diethylacetal (XII). Prepared from 5, 6-dimethyl-2-mercaptobenzimidazole [20] similarly to II. Yield 78.4%, viscous oil, soluble in organic solvents, insoluble in water.

Picrate, yellow crystals (precipitated from EtOH with water), mp 131–133°, then solidified and remelted at 270–272° (decomp.). Found: C 47.87; H 4.59; N 13.17; S 6.26%, calculated for $C_{15}H_{22}N_2O_2S \cdot C_6H_3N_3O_7$: C 48.18; H 4.81; N 13.38; S 6.13%.

3-Hydroxy-6, 6-dimethylthiazolino[3, 2-a]benzimidazole (XIII). Prepared similarly to IV (a) except that the reaction was run in 50% EtOH (1 hr reflux), yield 91.6%, mp 202-205° (decomp., ex EtOH). Found: C 59.88; H 5.36; N 12.76; S 14.57%, calculated for $C_{11}H_{12}N_2OS$: C 59.97; H 5.49; N 12.72; S 14.56%.

Picrate, mp 275-280° (decomp., ex EtOH). Found: N 15.72%, calculated for $C_{11}H_{12}N_2OS \cdot C_6H_3N_3O_7$: N 15.59%.

6,7-Dimethylthiazolo[3,2-a]benzimidazole (XIV). Prepares similarly to VI (a). Yield 97.3%, mp 156-157° (ex EtOH-water 1:1). Found: C 64.96; H 5.00; N 13.71; S 15.23%, calculated for $C_{11}H_{10}N_2S$: C 65.31; H 4.98; N 13.85; S 15.85%.

Picrate, mp 280-282° (decomp., ex AcOH). Found: N 16.21%, calculated for $C_{11}H_{10}N_2S \cdot C_6H_3N_3O_7$: N 16.24%.

2-Methyl-3-hydroxy-6,7-dimethylthiazolino[3,2-a]benzimidazole (XV). Prepared similarly to IX, yield 89.7%, mp 230-231° (decomp., precipitated from dimethylformamide with water). Found: C 61.60; H 5.90; N 11.63; S 13.20%, calculated for $C_{12}H_{14}N_2OS$: C 61.51; H 6.02; N 11.95; S 13.69%.

2,6,7-Trimethylthiazolo[3,2-a]benzimidazole (XVI). Prepared similarly to VI (a) (1 1/2 hr reflux). Yield 92.5%, mp 199-200° (ex EtOH-water, 1:1), found: C 66.95; H 5.58; N 13.04; S 14.47%, calculated for $C_{12}H_{12}N_2S$: C 66.63; H 5.59; N 12.95; S 14.82%.

Picrate, mp 227-228° (decomp., exploded in capillary, ex AcOH). Found: N 15.61%, calculated for $C_{12}H_{12}N_2S \cdot C_6H_3N_3O_7$: N 15.72%.

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